Sin3a regulates epithelial progenitor cell fate during lung development.

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Public Summary:
Embryonic lung development proceeds through a highly regulated process of epithelial growth and branching. Multipotent endodermal progenitor cells give rise to all epithelial cell types that line the airspaces of conducting airways and gas-exchange regions of the postnatal lung. We used genetically modified mouse models to show that Sin3a is a critical determinant of progenitor cell function; its loss within early lung endoderm completely blocked progenitor cell expansion leading to defects in lung development. These studies provide novel insights into the molecular circuitry that regulates the behavior of multipotent stem cells of the developing lung.

Scientific Abstract:
Mechanisms that regulate tissue-specific progenitors for maintenance and differentiation during development are poorly understood. Here, we demonstrate that the co-repressor protein Sin3a is crucial for lung endoderm development. Loss of Sin3a in mouse early foregut endoderm led to a specific and profound defect in lung development with lung buds failing to undergo branching morphogenesis and progressive atrophy of the proximal lung endoderm with complete epithelial loss at later stages of development. Consequently, neonatal pups died at birth due to respiratory insufficiency. Further analysis revealed that loss of Sin3a resulted in embryonic lung epithelial progenitor cells adopting a senescence-like state with permanent cell cycle arrest in G1 phase. This was mediated at least partially through upregulation of the cell cycle inhibitors Cdkn1a and Cdkn2c. At the same time, loss of endodermal Sin3a also disrupted cell differentiation of the mesoderm, suggesting aberrant epithelial-mesenchymal signaling. Together, these findings reveal that Sin3a is an essential regulator for early lung endoderm specification and differentiation.